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Novel Protein Kinase Targets in Vascular Smooth Muscle Therapeutics

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Abstract

Many signaling factors have been identified over the years that serve as mechanistic foundations for the pathogenesis and/or maintenance of cardiovascular disease (CVD). Of these, cyclic nucleotide-driven protein kinases in vascular smooth muscle (VSM) are of essential importance. Comprised primarily of cyclic AMP-dependent and cyclic GMP-dependent protein kinases, these ubiquitous signaling molecules have capacity to operate through numerous downstream effectors including vasodilator-stimulated phosphoprotein (VASP) to control aberrant VSM growth elemental to CVD. As more information is gathered regarding genetic, biochemical, molecular and cellular makeup of CVD including VSM cyclic nucleotide-dependent protein kinases and VASP, advances will be made in precision medicine by identifying more precise therapeutic targets to enhance clinical decision making.

Introduction

Protein kinases are highly ubiquitous and multi-functional and are capable of controlling cellular structure and function in a variety of tissues. In the cardiovascular system, vascular smooth muscle (VSM) is a major regulator of blood vessel function and homeostasis; however, abnormal growth of VSM is a key component in disease pathogenesis. The cyclic nucleotides cyclic AMP and cyclic GMP are essential second messengers that have been implicated in the control of cardiovascular disease (CVD). In turn, identifying molecular mechanisms for cyclic AMP and cyclic GMP including their downstream protein kinase effectors may provide insights into precise targets for therapeutic intervention. In this article brief synopsis is provided for cyclic AMP- and cyclic GMP-directed protein kinases, their regulatory roles during CVD, VASP as a primary effector protein, and their potential utility as targets for precision medicine.

Conflict of Interest Statement Nothing to declare.

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Protein kinases

Protein kinases can modulate target proteins in numerous ways and thus serve crucial roles in regulating cellular structure and function. Through phosphotransferase actions, protein kinases catalyze transfer of phosphates to protein substrates, thereby inducing conformational changes and/or altering functions and activities of target proteins [1**,2*]. Protein kinases act to phosphorylate either the -OH group of serine (Ser) and/or threonine (Thr), which constitute about 80% of the kinase family [3], or tyrosine (Tyr). Protein kinases represent one of the most ubiquitous and functionally diverse families in the human genome, constituting ~2% of all human genes with at least 518 members identified that target over 30% of all cellular proteins [2*,3,4]. Thus, they represent highly desirable drug targets for cardiovascular diseases (CVD), cancer and other pathologies and represent ~20% of all putative drug targets [5,6,7*].

A family of protein phosphatases (PPs) exist that serve to balance the phosphorylation status of kinase-targeted proteins in VSM. PPs catalyze transfer of phosphate groups from the phosphoprotein to water through their phosphotransferase abilities, thereby offsetting the actions of their complementary kinases. Removal of phosphate groups can serve to moderate conformational changes and/or cellular signals and functions elicited by kinase-driven phosphorylation and in turn can help regulate many cellular processes in pathologic VSM growth. We recently documented ability of global PPs and Ser/Thr-specific PPs to elicit control over abnormal VSM growth foundational to cardiovascular disorders [8,9].

Cyclic nucleotide signaling

Cyclic nucleotides represent one of the many genetic, biochemical, molecular and cellular elements identified over the years that can control protein kinase signaling and in turn, regulate cardiovascular function and processes. Comprised primarily of the cyclic purine nucleotides cyclic AMP and cyclic GMP, this family of biological second messengers operates largely through Ser/Thr protein kinases to control cellular processes in cardiac and vascular tissues. We have previously detailed key aspects of upstream generation of cyclic AMP and cyclic GMP as well as mechanisms for their downstream events including protein kinase-mediated (PKA, PKG, respectively) signaling in vascular tissue [10**,11**,12]. Notably, it is worthwhile to mention evidence of promiscuity and signaling crosstalk among many aspects of the otherwise distinct cyclic AMP and cyclic GMP signaling systems as these can directly affect their therapeutic potential. Contemporary discoveries using a variety of pharmacologic, genetic and molecular models have revealed lack of precision for upstream modes of protein kinase activation as well as downstream phosphorylation events [2*,10**,11**,12,13]. While Ser/Thr and Tyr protein kinases largely act on their preferred substrates, these enzymes can also be attracted to flanking residues of the canonical phosphoacceptor sites (Ser, Thr and/or Tyr); thus, the catalytic cleft of the kinase can interact with its preferred Ser, Thr or Tyr phosphoacceptor and also with their non-specific flanking regions, in turn binding to common recognition sequences among similar substrate family members thereby reducing overall kinase specificity. This protein kinase promiscuity affords broad impact of kinase signaling yet lends difficulty in ascertaining exact mechanisms and downstream and potentially therapeutic targets.

VSM anatomy and physiology

Before discussing the therapeutic potential of protein kinases in vascular disorders, even though we [14*] and others [15*] have recently detailed VSM anatomy, physiology and pathophysiology brief discussion here is warranted. Of the three concentric layers in most blood vessel walls, the middle layer (*tunica media*) is composed of spindle-shaped mononuclear VSM cells, a few macrophages and fibroblasts, and an interstitial matrix. Mature medial VSM cells are normally fully differentiated, contractile and quiescent. Physiologically, the VSM-rich medial wall provides structural support to blood vessels and is the main tissue controlling vasoconstriction and vasodilation and ensuing control of localized blood flow. Thus, the medial layer is crucial in the provision of nutrients and oxygen to essential tissues, in removal of metabolic by-products and carbon dioxide (CO₂), and in local blood pressure regulation.

Cardiovascular disease and VSM

Cardiovascular disease (CVD) has historically been the primary cause of death worldwide, accounting for ~30% of all deaths, and is considered a most significant global pandemic [16]. Of the many forms of CVD, coronary artery disease (CAD) accounts for more than half of all CVD-related deaths [16,17]. Although considerable efforts have been made at identifying, characterizing and controlling the many mechanisms that underlie CAD and CVD, outcomes from these studies have been incompletely effective and the number of individuals affected by these disorders is still rising. It is estimated that CVD prevalence in the United States will increase ~10%, coinciding with an estimated tripling of the economic burden of CVD, in the next 20 years [17]. Certainly, expanded efforts must be made to combat the wide-ranging and multifaceted mechanisms fundamental to CAD and CVD.

In that light, under abnormal disease conditions such as occurs in CVD and CAD medial VSM cells undergo conversion to a growth-promoting, synthetic phenotype capable of significant proliferation, migration, and matrix production [10**,11**,12,14*]. In the context of occlusive vascular disorders, these processes eventuate in and/or can exacerbate neovascularization and development of the growing luminal plaque, calcium deposition and plaque mineralization, outward expansion of the affected vessel with luminal enlargement, and sustained inflammation, in turn creating marked vessel stenosis and compromising regional blood flow. Given its central roles in the pathogenesis of CVD, CAD and other vascular disorders and its potential to serve as a rate-limiter for disease maintenance and/or progression, pathologic VSM growth presents a highly crucial and essential focus of particular therapeutic interest.

Cyclic nucleotide-driven protein kinases and VSM growth

Cyclic AMP and cyclic GMP largely operate through their canonical kinases, PKA and PKG, respectively. Some recent work has identified PKA and PKG as well as protein kinase C (PKC), protein kinase D (PKD) and AMP-activated protein kinase (AMPK) as clinically relevant modulators of pathologic VSM growth using varied experimental models and approaches [8,9,18,19**,20*,21; reviewed in 2*,10**,11**,12,14*]. In general these

Ser/Thr kinases can reduce pathologic proliferation and migration, moderate matrix synthesis and maintain matrix balance including cytoskeletal/focal adhesion elements, and enhance cellular apoptosis. We have also observed the importance of Ser/Thr-specific PPs in mediating these protein kinase activities and in maintaining balance of phosphorylation status [8,9]. We have used experimental animal models of pathologic vascular growth have verified ability of these kinases to regulate VSM growth in an intact system. Lastly, we have validated many of these observations in human coronary VSM cells, thereby supporting our basic science findings and adding therapeutic appeal to those observations.

Precision medicine for VSM-directed, cyclic nucleotide-mediated protein kinases

In 2015 President Barack Obama launched a new Precision Medicine Initiative aimed at preventing and treating human diseases with a focus on cancer through a personalized approach that takes into consideration individual variations in genetic makeup, lifestyle and the environment [22*]. Based on individualizes “OMICS” data such as epigenetics, genomics, (phospho)proteomics, and metabolomics, precision medicine proposes use of personalized information to target treatments in order to address each individual’s unique disease process(es). Thus, advancing our knowledge of these and perhaps other “OMICS” as well as their genetic, biochemical, molecular and cellular signatures highlights the potential of precision medicine for other disorders such as neurodegenerative diseases, diabetes, and CVD.

With this in mind and with regard to VSM-dependent CAD/CVD and the therapeutic significance of cyclic nucleotide-mediated protein kinases, several advances have been made over recent years that broaden our understanding of these multifaceted and complex mechanisms. More specifically, key molecular and cellular elements that underlie pathologic VSM growth as an underpinning of vascular disorders have been identified and characterized that could serve as potential therapeutic targets for individualized therapy. Consistent with a multi-faceted strategy for use of precision medicine in cancer [23], approaches targeting key cyclic nucleotide-driven protein kinase signals in VSM such as cell surface receptors and/or intracellular signaling factors are potentially feasible.

Signaling receptors

The major cyclic purine nucleotides, cyclic AMP and cyclic GMP, can be synthesized through receptor-mediated mechanisms including membrane-bound/membrane-associated receptors (including notably, by stimulatory G (G_s) protein-coupled receptor (GPCR) agonists) as well as through intracellular cascades that operate to stimulate adenylate cyclase. Conversely, cyclic AMP synthesis can be moderated through inhibitory G (G_i) GPCR signals [24,25]. Similarly, cyclic GMP can be generated via activation of membrane-bound guanylate cyclase through peptide hormones (such as atrial natriuretic factor) and/or through intracellular activation of soluble guanylate cyclase (by nitric oxide, carbon monoxide). These receptor-mediated processes for cyclic nucleotide generation could potentially serve as targets for upstream modulation and targeting in precision medicine, yet

considering the breadth and amplification of signal transduction cascades may suffer from lack of specificity and untoward effects.

Intracellular signaling factors

As one moves farther down a signaling cascade targeted therapies can often get more accurate and definitive. With that in mind, perhaps more precise modes for intervention of cyclic nucleotide-mediated protein kinases could involve targeting of key intracellular signaling events. Over the past decade or so we and others have identified a variety of intracellular targets of cyclic AMP and cyclic GMP and their kinase signals that play important roles in VSM pathobiology and that could serve as key precision medicine targets, and of these VASP is of particular interest. As a member of the Ena/VASP Homology (EVH) family of proteins, VASP can serve as an effector for both PKA and PKG, play critical functions in focal adhesion/cytoskeletal stability, and can be involved in various intracellular signaling pathways including integrin-extracellular matrix interactions. VASP operates as an anti-capping protein and promoter of actin polymerization and thus is capable of controlling cytoskeletal dynamics including, as we've documented recently, those involved in VSM cell proliferation and migration foundational to pathology [8,10**,11**,12,18,19**,21,26,27]. Intriguingly, our latest findings [19**] show ability of site-specific VASP phosphorylation to differentially regulate upstream PKG activity and ensuing growth control in VSM, thereby adding a unique mechanism for cyclic nucleotide-driven protein kinase signaling in vascular disease. In addition to its growth-regulatory capacities, Ser/Thr-phosphorylated VASP can control platelet function and adhesion and has anti-tumorigenic and anti-inflammatory properties [28,29,30]. Given the potential significance and utility of post-translational protein phosphorylation as a target in precision medicine [31], our recent observations that Ser/Thr-phosphorylated VASP may serve as a broad regulator of pathologic VSM growth provide evidence for its use in VSM-targeted precision medicine in CAD/CVD. A brief schematic depicting upstream generation of PKA and PKG, their common downstream effector VASP, and ensuing functional outcomes in VSM along with our recent observation [19**] of a positive feedback mechanism of VASP on PKG activity is shown in the summary figure.

Conclusions

Abnormal growth of VSM is fundamental to CVD pathogenesis, and among the many causative signaling factors that have been identified over the years PKA and PKG and their effectors are of critical importance. One such downstream target of PKA and PKG is cytoskeletal VASP which is instrumental in the regulation of aberrant VSM growth. By expanding our knowledge of the many facets of PKA and PKG (and perhaps other newly discovered cyclic nucleotide-driven kinases [32]) and their precise effectors including VASP in VSM, we can make inroads into the utility of precision medicine as a therapeutic tool to combat CVD.

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Highlights

- Abnormal vascular smooth muscle (VSM) growth is foundational to cardiovascular disease.
- Cyclic AMP and cyclic GMP operate primarily through PKA and PKG, respectively.
- PKA and PKG signal through many effectors including VASP during VSM growth.
- VASP may represent a novel target for precision medicine in cardiovascular disease.

Figure. Cyclic nucleotide-mediated, protein kinase-driven VASP as a target for precision medicine in vascular smooth muscle

The ubiquitous cyclic purine nucleotides cyclic AMP and cyclic GMP activate their predominant Ser/Thr kinases PKA and PKG, respectively, which target numerous effectors including focal adhesion cytoskeletal vasodilator-stimulated phosphoprotein (VASP) in vascular smooth muscle (VSM). VASP can operate to normalize underlying mechanisms of VSM pathology including aberrant cell proliferation and migration, altered extracellular matrix balance, and enhanced apoptosis, making it an attractive target for therapeutic intervention. Recent observations from our lab [18] also lend credence for positive feedback of VASP on upstream PKG activity in VSM. PKA and PKG as upstream activators and VASP as perhaps a more selective downstream target all hold promise for precision medicine in VSM in the context of cardiovascular disorders.